(19) Europäisches Patentamt
Europ an Patent Office
Office européen des brevets

(11) Publication number: **0 349 235**
A2

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 89306442.8

(22) Date of filing: 26.06.89

(51) Int. Cl.4: A61K 31/715 , A61K 33/10 , A61K 33/06 , //A23L1/30, (A61K31/715,31:455,31:19, 31:375),(A61K33/10,33:06, 31:715,31:455,31:19,31:375), (A61K33/06,31:715,31:455, 31:19,31:375)

(30) Priority: 28.06.88 US 212715

(43) Date of publication of application: 03.01.90 Bulletin 90/01

(84) Designated Contracting States: CH DE FR IT LI NL SE

(71) Applicant: HAUSER-KUHRTS, INC.
310 Olive Street
Santa Barbara California 93101(US)

(72) Inventor: Kuhrts, Eric H.
903 Park Lane
Santa Barbara California 93108(US)

(74) Representative: Perry, Robert Edward et al
GILL JENNINGS & EVERY 53-64 Chancery Lane
London WC2A 1HN(GB)

(54) **Niacin-containing composition and its therapeutic use.**

(57) An antihyperlipidemic pharmaceutical or dietary supplement compositon for oral use consisting essentially of a combination of niacin and guar gum, and a method of lowering cholesterol levels with such oral pharmaceutical composition, or by the simultaneous oral administration of the active ingredients thereof, which eliminates the usual undesirable flushing and itching side effects of niacin while effectively lowering cholesterol levels, especially LDL cholesterol levels, is disclosed.

EP 0 349 235 A2

NIACIN-CONTAINING COMPOSITION AND ITS THERAPEUTIC USE

This invention relates to antihyperlipidemic pharmaceutical or dietary supplement compositions containing niacin, and their use in treating hyperlipidemic conditions.

Novel aspects of the invention are:

An oral antihyperlipidemic composition of nicotinic acid, characterised by reduced flushing effect, comprising as active ingredients nicotinic acid and guar gum; such a composition wherein the composition contains at least 50 mg of nicotinic acid; such a composition wherein the amount of nicotinic acid is at least about 50 mg and the amount of guar gum is at least 250 mg; such a composition wherein the amount of nicotinic acid is at least about 50 mg and the amount of guar gum is at least 400 mg, in capsule or tablet form; such a composition wherein the amount of nicotinic acid is at least about 50 mg and the amount of guar gum is at least about 400 mg, comprising also an antacid; such a composition comprising a physiologically-acceptable magnesium salt; such a composition comprising an orally-ingestible non-toxic mineral salt capable of dissolution in the gastric fluid; such a composition wherein the mineral salt is selected from the group consisting of calcium carbonate, magnesium carbonate, and potassium carbonate; such a composition wherein the active ingredients are in powder form and comprising also a quantity of a food-grade acid in powder form which is effective in extending the time for gelation of the resulting mix upon addition of water; such a composition wherein the food-grade acid is selected from the group consisting of citric acid, ascorbic acid, tartaric acid, and malic acid; and such a composition comprising about 400-500 mg guar gum, about 80-100 mg niacin, and about 80-100 mg magnesium carbonate.

GENERAL DESCRIPTION OF THE INVENTION

The invention, in short, comprises the combination with niacin of guar gum, both of which are known to be effective antihypercholesterolemic agents, with the resulting effect that an extremely effective oral antihypercholesterolemic combination is provided, preferably in a single-dosage unit form. Alternatively, the two active ingredients may be orally administered simultaneously although administration of both together in a combination composition is preferred. In addition to the desired and augmented antihypercholesterolemic effect of the combination and combination therapy of the present invention, the usual cutaneous flushing, resulting in itching or prickling of the skin, as well as bright-red blushing, which ordinarily results from harmless dilation of the skin capillaries in the course of niacin therapy and which frequently manifests itself even at a niacin dose as low as 50 mg, has unpredictably been found to be greatly reduced or essentially eliminated when the niacin is administered or ingested in combination with the guar gum, the ratio of the guar gum fibers to the nicotinic acid preferably being approximately five parts of fiber to one part of nicotinic acid on a weight basis, although broader ranges are of course effective. Advantageously, a metal salt which is soluble in the gastro-intestinal fluids is provided as a buffer or to enhance dispersability of the guar gum. Morever, the inclusion of a magnesium salt which is soluble in the gastro-intestinal fluids also appears to reduce still further the flushing, itching, and other usual side effects of the niacin therapy, and is accordingly preferred. The exact form in which the active ingredients are orally administered is not important, so long as the objectives of the invention are obtained. The active ingredients may take the form of the usual tablets, capsules, suspensions, dispersions, elixirs, syrups, or the like, whether administered singly or in combination, and may moreover be provided in the usual form for dietary supplements involving inclusion of a fibrous material, such as in capsules, drink mixes, breakfast foods, or the like, especially when metallic salts assisting with the internal dispersion of the guar gum are included and/or when acids, and especially organic acids such as citric, ascorbic, malic, and tartaric are included not only to delay gelation of the guar gum when the active ingredients are presented in the form of a drink mix but also to add a pleasant palatable flavor thereto.

DETAILED DESCRIPTION OF THE INVENTION

The following Examples are given to illustrate the invention, but are not to be construed as limiting.

Example 1

A composition is prepared according to the following formula:
Guar gum (Cyamopsis Tetragonoloba) 400-500 mg
Niacin (nicotinic acid) 80-100 mg

These ingredients, guar gum and niacin, are blended together and encapsulated in a hard gelatine capsule. A lubricating agent may as usual be used to facilitate encapsulation. This formula can be conveniently orally ingested at an effective therapeutic dose of five (5) capsules, preferably three (3) times a day.

At a dosage of five (5) capsules, the amount of active ingredients is 2,000-2,500 mg of guar gum and 400-500 mg of niacin, close to the preferred ratio of five parts of fiber to one part of niacin.

When this dosage is taken three (3) times daily, the total amount of guar gum is 6 to 7.5 grams and the amount of niacin is 1.2 1.5 grams, an effective dosage regimen although involving less than the usually recommended daily dose of niacin when used alone.

Example 2

In addition to the guar gum and the niacin in the amounts set forth in Example **1**, magnesium carbonate is included in the composition in an amount of 80-100 mg per capsule. At a therapeutic dose of five (5) capsules, this makes the amount of magnesium carbonate 400-500 mg and, at a TID regimen, the number of capsules 15 per day, the amount of magnesium carbonate ingested then being 1.2 - 1.5 grams.

Example 3

In additional formulations, calcium carbonate, aluminum hydroxide, or other physiologically-acceptable mineral salt is employed as buffer or antacid.

Example 4

A further specific Example of a formulation according to the present invention is the following:

Guar gum	470 mg
Niacin	74 mg
Magnesium carbonate	74 mg

PHARMACOLOGICAL AND CLINICAL EVALUATION

A. The cholesterol-lowering properties of the combination composition of Example 1 are examined clinically at a dosage of five (5) capsules TID, making 15 per day in all, taken at mealtime, over a period of two (2) weeks.

This is equivalent to approximately 7.05 grams of guar gum and 1.11 grams of niacin per day.

The results of the clinical study are as follows:

Participant	Total Cholesterol Before mg/dl	Total Cholesterol After mg/dl	Difference mg/dl	% Reduction
M.T.	264	210	-54	20.5
M.A.	318	256	-62	19.5
K.E.	262	220	-42	12.2
W.J.	387	293	-94	24.3
O.M.M.	236	212	-24	10.2

The formulation of the invention greatly reduces the side effects of niacin, such as cutaneous flushing, resulting in itching or prickling of the skin and bright-red blushing, which is a result of the dilation of the skin capillaries and which occurs in most individuals at the beginning of treatment and whenever the dosage is increased.

B. In similar clinical tests using the formulation set forth in Example 2, the results are essentially identical. However, the amount of flushing, itching, prickling, and blushing, as subjectively experienced by the subjects in the test panel themselves and as observed by other members of the test panel, is unpredictably still further reduced. In addition, the amount of gastro-intestinal distress is substantially reduced due to the buffering effect of the magnesium carbonate employed.

C. According to the present invention, a further cholesterol-lowering study is carried out employing the combination compositions of the present invention according to Example 4. In the present study, each participant orally ingests a niacin combination composition according to the present invention having the following formula:

Dose: Five (5) capsules, TID (3 times a day)

Each capsule containing:

74 mg	niacin
470 mg	guar gum
74 mg	magnesium carbonate

At a dose of five capsules, the amount of niacin is 370 mg, the amount of guar gum 2.35 g, and the amount of magnesium carbonate is 370 mg. At a dosage regimen of three times per day (TID) the amount of niacin is 1.11 grams, the amount of guar gum is 6.9 grams, and the amount of magnesium carbonate is 1.11 grams.

This dosage produces results equivalent to those set forth under "A", including a reduction in total cholesterol which averages 20.37% in the test panel of five (5) subjects, which is nearly equivalent to the results obtained using a nicotinic acid dosage of three (3) grams per day. In other words, in the present combination, a daily dosage of niacin which amounts to one-third of the daily dose, usually employed for niacin alone, is capable of lowering total cholesterol to approximately the same degree, and without the intolerable side effects ordinarily produced by niacin alone at such dosage levels.

Alternatively, the clinical study can be observed by administering the active ingredients nicotinic acid and guar gum simultaneously. As already pointed out, calcium carbonate or other mineral carbonate can be substituted for the magnesium carbonate, although a magnesium salt such as magnesium carbonate, magnesium oxide, or magnesium hydroxide, but preferably magnesium carbonate, produces unobvious and clear-cut advantages, as already set forth.

In an extension of the clinical evaluation set forth in the foregoing under "C", subject No. 1 after seventeen (17) days and subject No. 2 after eighteen (18) days were evaluated from the standpoint of effect upon different types of blood components, the following cumulative summary report indicating for No. 1 as follows:

	Day 1	Day 17
Cholesterol	387	293 MG/DL
Triglyceride	357	198 MG/DL
HDL-C	39	42 MG/DL
LDL-C	277	211 MG/DL
VLDL-C	71	40 MG/DL
LDL-C/HDL-C	7.0	5.0
Chol/HDL-C	9.9	7.0

With respect to subject No. 2, the following cumulative summary report shows the results after eighteen days according to the suggested five (5) capsule dosage TID using the combination composition of Example 4 hereof.

	Day 1	Day 18
Cholesterol	264	210 MG/DL
Triglyceride	101	70 MG/DL
HDL-C	53	56 MG/DL
LDL-C	191	140 MG/DL
VLDL-C	20	14 MG/DL
LDL-C/HDL-C	3.6	2.5
Chol/HDL-C	5.0	3.7

From the foregoing, it is clear that in both cases the HDL cholesterol percentage was increased while the LDL cholesterol and the VLDL cholesterol was substantially reduced, as well as total cholesterol and triglyceride content, and that the ratios of LDL-C to HDL-C and Chol/HDL-C dropped considerably.

Extremely noteworthy is the improved LDL/HDL ratio, which is indicative of a reduced risk for heart disease according to established interpretation of such results.

According to the practice of the art, the niacin or nicotinic acid may be provided as such or in the form of a prodrug thereof, numerous of which are presently available and which break down, to a greater or lesser extent upon ingestion, to provide nicotinic acid in the system of the subject orally ingesting the same for reduction or control of cholesterol levels in the said subject. Representative prodrugs of this type are derivatives of nicotinic acid, especially esters, amides, and the like, and many of these prodrugs are also subject to the same side effects as niacin itself, namely, the production of the undesirable and sometimes intolerable side effects of flushing, itching, and the like and, to the extent that these prodrugs do provide nicotinic acid upon ingestion, as well as the undesirable side effects of niacin previously mentioned, they may be employed according to the present invention in lieu of niacin itself, the method and combination compositions of the present invention providing effective cholesterol-lowering effect as well as reduction or essential elimination of the undesirable effects of niacin when such a prodrug is employed just as in the case of the employment of niacin itself.

As already stated, in a particularly preferred embodiment according to the present invention, a physiologically-acceptable soluble magnesium salt is administered simultaneously together with the active ingredients according to the present invention, namely, niacin and guar gum, and most preferably in a combination composition together therewith. The inclusion of the physiologically-acceptable magnesium salt appears to still further reduce the flushing and related side effects of the niacin and such magnesium salt may illustratively but not limitatively be or comprise magnesium carbonate, magnesium chloride, magnesium oxide, magnesium hydroxide, or any other physiologically-acceptable salt of magnesium with either a mineral or organic acid which is soluble, that is, capable of dissolution in the gastric fluids.

According to one preferred embodiment of the present invention, the active ingredients, namely, niacin and guar gum, are provided in granular form for addition to water to provide a drinkable form of oral administration. When employed in this form, a quantity of a food-grade acid, also in powder form, which is effective in extending the time for gelation of the resulting mix upon addition of or to water, is also preferably supplied concurrently or simultaneously with the aforementioned active ingredients and, in the most preferred form, is provided in the form of a granular mix together with the other active ingredients so as to provide a combination granular mix composition. When the composition and the method of the present invention are so constituted and/or administered, the food-grade acid employed is preferably citric

acid, ascorbic acid, tartaric acid, or malic acid, which provides a tasty and palatable flavor while at the same time providing effectiveness for extending the time for gelation of the resulting mix upon the addition of or to water.

In another preferred embodiment according to the present invention, an orally-ingestible non-toxic mineral salt capable of dissolution in the gastric fluids is also administered simultaneously with the active ingredients, namely, niacin and guar gum, preferably in a combination composition therewith and, when the active ingredients according to the present invention are so constituted or administered, the orally-ingestible non-toxic mineral salt capable of dissolution in the gastric fluids assists with more rapid and complete internal dispersion of the guar gum in the gastrointestinal tract, and is preferably selected from the group consisting of calcium carbonate, magnesium carbonate, and potassium carbonate.

It is therefore seen that the present invention provides an oral antihyperlipidemic composition of nicotinic acid (niacin) characterized by reduced and related flushing effects comprising as active ingredients nicotinic acid and guar gum, which is effective in lowering of cholesterol levels, especially LDL cholesterol levels, without the usual undesirable flushing, itching, and related side effects of niacin, and a method of lowering cholesterol levels by employment of such an oral pharmaceutical or dietary supplement composition, or by the simultaneous oral administration of the active ingredients thereof, all having the unpredictable and highly advantageous characteristics and effects as more fully set forth in the foregoing.

Claims

1. A composition comprising guar gum, and nicotinic acid or a precursor which can be broken down on or following ingestion to yield nicotinic acid, for simultaneous, combined or successive antihyperlipidemic use.

2. A composition which comprises at least 50 mg nicotinic acid or a precursor and at least 250 mg guar gum, e.g. in tablet or capsule form.

3. A composition of claim 2, which comprises at least 400 mg guar gum.

4. A composition of claim 2 or claim 3, wherein the active ingredients are in granular form, and comprising also a quantity of a food-grade acid in powder form which is effective in extending the time for gelation of the resulting mix upon addition of water.

5. A composition of claim 4, wherein the food-grade acid is selected from citric acid, ascorbic acid, tartaric acid and malic acid.

6. A composition of any preceding claim, comprising also an orally-ingestible non-toxic mineral salt capable of dissolution in gastric fluid.

7. A composition of any preceding claim, comprising also a physiologically-acceptable magnesium salt.

8. A composition of claim 6 or claim 7, wherein the salt is selected from calcium carbonate, magnesium carbonate and potassium carbonate.

9. A composition of claim 2, comprising 400-500 mg guar gum, 80-100 mg niacin, and 80-100 mg magnesium carbonate.

10. A composition of any preceding claim, comprising also an antacid.